The Wesley M. Carpenter Lecture

MUSCULAR PAIN IN INTERMITTENT CLAUDICATION*

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The term intermittent claudication seems first to have been used by Bouley in 1831 to describe a condition of lameness in the horse, developing after a short period of exercise, and caused by obliteration of the main vessels of the limb; his account was followed by that of other veterinarians. In 1846 Brodie and later Charcot noticed a similar condition in human patients suffering from senile arteritis or from aneurysm of the common iliac artery. Erb's collection of clinical and pathological observations led to wide recognition of the malady and served to establish that obstructive arterial disease is the usual anatomical defect and that lameness developing during exercise results usually from pain. It is with the origin of this pain that the present lecture deals.

Charcot's view was that loss of blood supply leads to cramp of the muscles, regarding this cramp as comparable to cadaveric rigidity. Marinesco recognised that the blood supply to the muscles was adequate during rest but not during work. Goldflam and Erb held similar views but referred to the possibility of the pain arising in the arteries themselves. Erb, too, had in mind the possibility of a functional element in the form of vascular spasm, an idea

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which has received support from other writers and has considerably influenced subsequent writings.

The idea that cramp is present when the moving limb becomes painful sprang from early accounts of general rigidity in the affected limb during the attack both in the horse and in man. Usually, however, cramp in the sense of tonic contraction is not described and it is manifest, both from past records and from numerous personal observations, that cramp is unessential to the production of pain. Thus it is not at all clear as yet how ischæmia leads to pain.

In investigating the pain of intermittent claudication, an important step is taken when it is recognised that the pain experienced by our patients can be reproduced exactly in normal limbs to which the blood supply is previously shut off. This conclusion has been formed by Zak, Brown and Allen and others. It is so necessary to be certain of its truth before proceeding, that it has been examined thoroughly in observations including a close comparison in the patient of the abnormal leg with the other leg, the latter being less affected or appearing normal. The muscles of the two legs are given work to do under strictly controlled conditions, and the time at which pain develops and the precise situation and character of this pain are noted. It is found that when the circulation to both limbs is obstructed and they are similarly exercised, pain arises in the two, normal and abnormal, at precisely the same time and in similar situations, and that the pain is of exactly the same kind in both limbs. It is also stated by the patient that the pain reproduced is exactly the same as that produced by walking exercise. In cases in which the disease in the abnormal limb is severe, it is a matter of indifference whether the circulation to this limb is artificially obstructed or not, exactly the same form of pain appears and, if it does not occur in the usual time period, it is not long delayed. It has also been shown that pain having precisely similar characteristics occurs in normal subjects when the circulation to the limb is obstructed and the mus-

cles are similarly worked. In saying that the pain has similar characteristics, reference is made to the fact that the pain is aching in quality; that it is a continuous pain and that, appearing under circulatory arrest, it continues so long as the bloodflow remains stopped; that the pain is accompanied by local tenderness; that it can be brought about in this or that site by throwing the strain particularly upon this or that group of muscles. Most important of all, the times taken for the pain to begin and to become intolerable are the same in all instances, normal and abnormal, provided that the circulation in the muscles is brought to the same state in all during exercise. These observations clearly prove that the problem of the pain studied is independent of a pathological state of the tissues from which it arises, and that in the patients it is purely a problem of disturbed circulation.

Once it is proved that the pain is identical in patient and in normal subject, the normal subject can be used for further investigation, and it becomes a matter of indifference whether the leg or the arm is used; most of our observations have been upon the forearm.

Theory of arterial spasm.

According to the view especially advocated by Zak, the pain of intermittent claudication is due to spasm of the arteries of the limb, the arterial spasm arising out of ischæmia. Actually this view may be disproved by a simple method. The limb is enclosed in a plethysmograph and the rate at which blood enters it is estimated by the method of Hewlett and Zwaluwenberg. The circulation to the limb is arrested and the arm is worked until severe pain arises in it; at this instant the circulation to the limb is released and the rate at which blood enters is again estimated; it enters at a velocity greatly in excess of the value for the resting limb and it enters at this increased velocity from the instant of release and while pain is still present. It is perfectly clear from these results that the idea that the vessels of the limb are in a state of spasm during the

period of pain is erroneous; on the contrary, they are dilated.

Pain the product of muscular contraction.

In further investigating the nature of the pain, a simple device in the form of an isometric recorder has been used. The movement mainly studied has been that of a simple grip, which involves the muscles of the thenar eminence and the muscles of the forearm. It is a movement that can be nicely controlled and is in other ways convenient, the amount of exercise taken is precisely known, the rhythm of movement being usually one contraction a second and the grip maximal or of lesser but known strength. Using this device and proceeding with the test from an adequate preliminary period of rest, the result of exercise with the circulation to the limb stopped is surprisingly constant in the same individual and from one individual to the next. While the beginning of pain may not be very sharply defined, the time at which it reaches its intolerable point is almost critical. It is about a minute and a quarter and it does not usually vary more than a few seconds in repeated tests; the result is so constant for a given set of circumstances that the test may be employed safely in testing the effects of varied circumstances.

A very remarkable fact is that the pain which develops on exercise, while the circulation is arrested, vanishes completely within 2 to 4 seconds of circulatory release, but if exercise ends and the circulation remains arrested, pain persists until the flow of blood returns. The pain persists during circulatory arrest substantially unchanged and at or about the particular intensity to which it has been brought (slight, moderate or severe) during the previous exercise. From these observations we have been led to conclude that the pain under consideration must be determined by a chemical (or physico-chemical) stimulus developed in the muscle mass during its exercise, and that the stimulus is a stable factor during the period of rest.

Lack of oxygen not the direct factor.

It is easy to show that the effect of lack of oxygen upon the nerve endings is not directly responsible for pain; thus, a preliminary period of 10 minutes complete obstruction of bloodflow to the limb, causing as it does considerable loss of oxygen, does not diminish the time taken for pain to appear in a succeeding period of exercise. Another and very conclusive experiment is the following. The usual test exercise is continued under circulatory arrest until pain appears and the time is noted. After a period of rest the test is repeated in exactly the same way but the exercise is stopped a few seconds before pain is anticipated. The pain does not develop even if the arterial occlusion is prolonged for a further 5 minutes. If the pain were attributable to lack of oxygen it is clear that at the instant exercise ended the amount of oxygen in the tissues would have declined almost to the necessary level. Yet although during the immediately succeeding period oxygen will still be used up rapidly, owing to the oxygen debt established by the muscles, no pain develops. Thus, the view that in this experiment pain fails to develop simply because oxygen deficiency is not carried far enough, is untenable.

Pain related to amount of exercise.

The relation of pain to the amount of exercise taken is easily demonstrated. Firstly, if the rhythm of the contractions remains constant but the tension developed is increased, the beginning of pain is correspondingly expedited; and, secondly, if the tension developed at each contraction is kept constant but the rhythm of contraction is doubled, then the period over which exercise has to be continued to produce pain is approximately halved. The relation of pain to the amount of energy expended is shown by these observations with much precision.

"Factor P".

From the experiments so far described, and from further evidence presently to be given, it is concluded that

when muscular exercise is taken in the absence of blood supply it leads to pain, and that the stimulus actually responsible for the pain arises directly or indirectly out of the contraction process; for reasons that will appear later we assume this stimulus to act in the tissue spaces. When muscle contracts, changes such as a release of metabolites occur within its fibres; an obvious possibility is that such metabolites diffuse out and constitute the stimulating agent in the spaces; this conclusion, however, is one that cannot be accepted finally as there are other possible explanations. So it becomes necessary for the moment to keep the relevant changes within and without the fibre as separate ideas, and we shall do so by calling the latter "factor P" because it is the stimulus to pain. So long as there is no bloodflow, "factor P" remains stable; it is cumulative, increasing with each muscular contraction and irrespective of time. It rises first to a level adequate to bring pain, then to higher levels associated with increased pain; being stable during circulatory arrest it maintains the pain between muscular contractions and after exercise has ceased.

Recovery.

The relief of pain on releasing the circulation is not to be interpreted as meaning complete recovery of the underlying process within the muscle fibre, but only that the accumulation of "factor P" has been reduced below the pain level. It can be shown that recovery takes longer; exercise is taken from rest with the circulation stopped and pain is noted to develop to the intolerable point in a given time period; the circulation is released and after a short period of rest is stopped again and the exercise repeated. If various periods of rest are allowed to intervene between tests, it is found that the shorter the period of rest the quicker intolerable pain appears in the subsequent test.

Muscular exercise with bloodflow free.

When exercise is undertaken with the circulation free

there may be a little ache in the arm, but pain of the character here studied does not arise; from this it is unnecessary to conclude that "factor P" fails to develop under these circumstances, since conceivably it rises with contractions and falls in the intervals, and thus fails to reach the pain producing level. From this standpoint it is important to observe that muscular exercise with free circulation shortens the period required to produce pain in the subsequent test.

It has just been shown that during muscular exercise with the circulation undisturbed, a process of accumulation relating to the development of pain occurs, although pain does not appear during that exercise. The accumulation in question is regarded as happening within the muscle fibre; it is not an accumulation of "factor P". From this standpoint a curious phenomenon which we term "latent pain" is relevant. If exercise is undertaken with the circulation free but the bloodflow is arrested at the instant exercise ends, there is no pain, but pain develops after a latent period more or less prolonged and may become not only distinct but severe. This latency cannot be attributed to latency in the formation of "factor P"; for no such delay is suggested by other relevant observations. If the circulation is arrested, "factor P" accumulates to given levels while exercise is proceeding, and is maintained at these levels, whether they are sufficient to be pain producing or not, if exercise ends and the circulatory arrest continues. But if the blood is flowing during exercise, then, although up to a point the chemical changes in the fibre will be cumulative, "factor P" will not necessarily accumulate correspondingly in the tissue spaces or to a level adequate to stimulate the nerves themselves. The latent period from occlusion to the appearance of pain in the experiment above cited is a period during which "factor P" is rising in the tissue spaces to a level corresponding to the state of the fibre. Thus our fuller hypothesis takes the form that a product of muscular contraction is directly or indirectly responsible for pain; that, when successive mus-

cular contractions occur in the absence of bloodflow, the state of the muscle alters progressively and that *pari passu* "factor P" accumulates in the tissue spaces; but that when the muscular contraction occurs in the presence of bloodflow, although the same change happens in the muscle fibre, "factor P" cannot rise to the corresponding level in the tissue space. Quick disappearance of the pain of exercise on release of the circulation is to be interpreted as due to the prompt reduction of the level of "factor P" in the tissue spaces, and not to recovery of the muscle mass as a whole. The ordinary failure of pain to appear in muscular exercise with intact circulation may be attributed to adequate interchange between tissue space and vessel in which bloodflow is rapid.

The purpose of hypothesis is to provide an explanation of the facts, to clear our conceptions, and to act as a basis for future observation. The hypothesis as it stands is directly applicable to cases of intermittent claudication and helps us to understand the phenomena these display. Upon its basis simple tests can be devised that are serviceable in ascertaining the degree in which blood supply to the muscles is deficient. Thus the time taken for pain to develop in a limb under standard conditions of work, and its relation to the time taken when the circulation to this limb is artificially and completely arrested, is clearly important. Another important gauge in similar tests is the rate at which pain subsides from the intolerable point on releasing the circulation, for the greater the returning bloodflow, the quicker will normal conditions become reestablished in the tissue spaces.